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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,409	03/25/2004	Christian Viskov	03806.0579	5110

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EXAMINER	
KHARE, DEVESH	
ART UNIT	**PAPER NUMBER**
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/808,409	VISKOV ET AL.	
	Examiner	Art Unit	
	Devesh Khare	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/23/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *10-41,44,45,48-61 and 66-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,42,43,46,47 and 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This application claims benefit of EPO 04290791.5 filed 03/24/2004.

In a response filed on 10/23/2006, the applicant elected Group II, claims 1-9, 42, 43, 46, 47 and 62-65.

Response to Election with Traverse

Applicant's election with traverse of the process for preparing LMWH and a method for determining the oligosaccharide content thereof defined by Group II (claims 1-9, 42, 43, 46, 47 and 62-65) dated 10/23/2006 is acknowledged. The traversal is on the ground(s) that "the search and examination of Groups I, II and III would not impose a serious burden". This is not found persuasive because the applicants claims encompass three distinct inventions of different class and subclass: I. Claims 39-41,44,45 drawn to a LMWH (low molecular weight heparin) and a composition having low or free of glycoserine, classified in classes 514, 424 and 536, subclass various.

II. Claims 1-9, 42, 43, 46,47 and 62-65 drawn to a process for preparing LMWH of Group I and a method for determining the oligosaccharide content thereof, classified in class 536, subclasses various.

III. Claims 10-38, 48-61 and 66-70, drawn to a method for determining/quantifying glycoserine content in heparin and a method of monitoring glycoserine in heparin, classified in 536 and 435, subclasses various, which would be burdensome to the examiner because the search of product; process and the method of detection of said product is not co-extensive. The requirement is still deemed proper and is therefore made FINAL.

Claims 10-41, 44, 45, 48-61 and 66-70 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

An action on the merits of claims 1-9, 42, 43, 46, 47 and 62-65 is contained herein below.

Minor objections

Claims 43 and 62 are objected to because of the following informalities:

(1) In claim 43, line 3, the term ":" separating the phrases "comprising" and "depolymerizing" is not required therefore should be deleted.

(2) In claim 62, at least one oligosaccharide is chosen from MM=511, MM=588 and MM=690. The MM=511 is not an oligosaccharide, the specification on page 26 discloses MM=511 as a disaccharide. Therefore, MM=511 should be deleted from the oligosaccharide Markush group.

Appropriate correction is required.

35 U.S.C. 112, second paragraph rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 42, 43, 46 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(1) Claims 1, 42, 46 and 47 contains the recitations "a manufacturer of"; "exclusive of commercially..... application"; and "by a manufacturer.....and assigns". Where a recitation is used in a claim as a limitation to identify or describe a particular material or product or process, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since said recitation cannot be used properly to identify any particular material or product or process. Thus, said recitation does not identify the process associated with the recitation. In the present case, the recitation is used to identify/describe the commercially available LMWHs regulated by the USFDA and Aventis Pharma SA, its fully owned subsidiaries and, accordingly, the process or identification/description is indefinite.

(2) In claims 42, 43, 46 and 47, in the phrase "depolymerization.... according to a process" in the absence of the specific process or method used in the depolymerization step, render the claims indefinite wherein applicant fails to articulate the specific process or method in the depolymerization step. The specification discloses the depolymerization as fragmentation, chemical and enzymatic depolymerization and other methods of preparing fragments of heparin, including without limitation fractionation (see page 11, [032]) however the specific process or method used in the depolymerization step of the instant claims is unclear.

(3) Claims 1a, 42a, 43, 46a and 47 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted

elements are: In the purification of the heparin by oxidation with permanganate salt at a temperature ranging from 35-90^0 C the reaction time or duration is not disclosed; the reaction fails to identify a critical element of the reaction: "how long the permanganate salt is reacted with heparin" when heparin is heated with permanganate salt in the oxidation step to obtain glycoserine-free or low glycoserine heparin.

Claims which depend from an indefinite claim which fail to obviate the indefiniteness of the claim from which they depend are also seen to be indefinite and are also rejected for the reasons set forth supra.

35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Claims 1-9, 42, 43, 46, 47 and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bush et al. (Bush)(U.S. Patent 3,135,660) in view of Van Boeckel et al. (Boeckel)(U.S. Patent 5,451,668) in combination with Weitz et al. (Weitz) (U.S. Patent 6,075,013).

Bush teaches a method for decolorizing heparin solutions by subjecting the solutions to the action of certain oxidizing agents such as permanganate (as the potassium, sodium or other salt) (col.1, lines 13-15; 45-48; and 62-65). Bush discloses that the reaction temperature may vary from room temperature or below to as high as at least 70^0 C (col.2, lines 22-24). Bush discloses that during said reaction the permanganate is reduced and precipitated and removed followed by precipitation of the heparin (col.2, lines 29-31). Bush also discloses the use of 10% by weight of potassium permanganate at 75^0 C on heparin (col.2, Example 1). Furthermore, Bush discloses that amount of potassium permanganate can vary between 1-30% by weight depending on the quality of the crude heparin used; the higher the degree of purity, the less permanganate is required (col.3, lines 14-16 and 21-24). Bush discloses that the viscosities of said treated heparin are appreciably lower than untreated solutions and may be used in smaller and less painful needle when giving injections of the purified heparin solutions to patients (col.4, lines 27-34). While Bush does not specifically teach the use of permanganate salts to decolorize the low molecular weight heparin (LMWH, 3000-8000 Daltons) or ultra-low molecular weight heparin (ULMWH, 1500-3000 Daltons), the person or ordinary skill in the art at the time of the invention would have certainly found it obvious to have used permanganate salt with a reasonable expectation that such salts can be inherently useful to decolorize LMWH or ULMWH by removing or reducing the glycoserine moiety of said heparin by said oxidation as claimed in claims 8 and 9. The method of oxidation of the Bush reference differs from applicant's method in that Bush

does not suggest further depolymerization of heparin obtained after the oxidation process and determination of the oligosaccharide content thereof.

Boeckel teaches a method of degradation or depolymerization of heparin wherein the glycoside bond between a glycosamine unit and an uronic acid unit is broken, a double bond between C-4 and C-5 being formed in the newly generated non-reducing end (col. 1, lines 10-15). Boeckel discloses that said method can be achieved with the aid of enzymes such as glucuronidases or with a bleaching agent such as permanganate (col.1, lines 31-33 and 48-54). Boeckel also discloses the degradation of heparin with heparin lyase (col.2, line 4). Boeckel discloses the heparin degradation with heparin lyase to obtain desired mean molecular weight of heparin (col.2, Example 1). Boeckel discloses that depolymerized heparin can be subjected to oxidation using sodium permanganate solution (col.3, Example 1, bleaching). Furthermore, Boeckel discloses that enzymatically-degraded heparin can be heated with sodium permanganate solution (40% by weight) at 80^0 C for 30 min to obtain bleached heparin fragment (col.3, Example 3).

With regard to the decolorized heparins such as fraxiparin, fragmin, innohep, normiflo, embollex, fluxum, clivarine, hibor and enoxaparin of claims 42, 46 and 47, it would be within the scope of the artisan in this art to obtain them through routine experimentation in view of the oxidation and depolymerization of heparin taught by the prior arts set forth above, in the absence of unexpected results with a particular combination.

With regards to claims 62-65, Weitz teaches a process wherein the unfractionated heparin is depolymerized to yield low molecular weight heparin (col.8, lines 22-26) and further can be detected or isolated using a chromatography process such as gel permeation chromatography, HPLC, ultrafiltration, size exclusion chromatography etc. (col.7, lines 47-63). Weitz also discloses various depolymerization processes of heparin such as chemical and enzymatic reactions (col.8, lines 52-62). Weitz discloses that molecular weight characteristics of the depolymerized heparin fractions can be determined using standard techniques such as GPC-HPLC or HPSEC-MALLS by detecting their molecular mass (col.10, lines 15-30). With regard to the use of a chromatography process to detect oligosaccharide fractions having MM=588 or MM=690 in a depolymerized heparin sample. It would be within the scope of the artisan in this art to detect them using techniques such as GPC-HPLC, which also employs external or internal calibration and internal standard, through routine experimentation, in the absence of unexpected results with a particular combination.

Therefore, one of ordinary skill in the art would have found the applicants claimed processs for preparing at least one decolorized heparin product comprising the oxidation and depolymerization of heparin and a method for determining oligosaccharide content of a depolymerized heparin sample, to have been obvious at the time the invention was made having the above cited references before him. Since Bush teaches oxidation of heparin for decolorizing heparin solutions by subjecting the solutions to the action of certain oxidizing agents such as permanganate (as the

potassium, sodium or other salt); Boeckel teaches a method of degradation or depolymerization of heparin wherein the glycoside bond between a glycosamine unit and an uronic acid unit is broken, a double bond between C-4 and C-5 being formed in the newly generated non-reducing end ; and Weitz teaches that molecular weight characteristics of the depolymerized heparin fractions can be determined using standard techniques such as GPC-HPLC or HPSEC-MALLS by detecting their molecular mass, one skilled in the art would have a reasonable expectation for success in combining said references to accomplish a process for preparing at least one decolorized heparin product and a method for determining oligosaccharide content of a depolymerized heparin sample. The motivation for doing so is provided by Bush, which suggests that the viscosities of said treated heparin are appreciably lower than untreated solutions and may be used in smaller and less painful needle when giving injections of the purified heparin solutions to patients (col.4, lines 27-34).

Any inquiry concerning this communication or earlier communications from the

Examiner should be directed to Devesh Khare whose telephone number is (571)272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang, Supervisory Patent Examiner, Art Unit 1623 can be reached at

(571)272-0627. The official fax phone numbers for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Devesh Khare, Ph.D.,J.D.
Art Unit 1623
January 22, 2006